Social interactions in health and psychosis

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Chapter 1

General Introduction

One early evening at university, most colleagues had already gone home, I encountered a man in the entrance hall. He asked: "Excuse me, could you help me please? I am participating in an experiment and I don't know where to go."

How do we react to others, familiar or unknown to us? We judge on what we see, interpret all the signals around us: how the person looks, behaves, the situation and the environment we are in; we link the information to our own experience; and finally decide to react in a certain way. Many factors shape our thoughts and behaviour towards other people. Reactions could therefore be manifold: I might be scared, being alone, thinking he might want to hurt me; I might think the question was just a way of getting in contact with me, because he had been watching me for some time; I might reply: "I don't know, I can't help you" and continue with my pursuits; or I might trust this person, respond to his question (and needs), and try to help him find the experiment room. This last option would cost me very little, maybe a few minutes of my time, but yields the opportunity to build a positive interaction with the other person, based on initial trust.

From the minute we are born, we humans engage in social interactions, building relationships with others. With development, we become more aware of other people, and proficient in interpreting and inferring their gestures, expressions and desires. Depending on the relationship, we are even willing to set aside our own interest for the benefit of another person, or for the common interest of a social group. These social interactions require social cognition, the ability to perceive the intentions and dispositions of others, to construct representations of the relation between the other and the self, and to use those representations to guide social behaviour (Couture, Penn, & Roberts, 2006). Social cognition comprises processes like mentalising or theory of mind (ToM), empathy, and emotion perception. Mentalising or ToM is the ability to understand the mental states and perspectives of others, and to make attributions about their intentions and beliefs. Empathy refers to the ability to understand and experience what others feel, and emotion perception is the process of recognising expressed emotions in the faces of others. Social cognitive skills develop with brain maturation, and in interplay with social environment: Social encounters and environmental influences, shape the brain, which in turn changes the reactions to the surrounding factors. Growing up in densely populated areas may impact on the nature of social encounters and interactions. Large individual differences exist, and patients with psychopathology often show deficits in these processes.

Psychosis is characterised by marked problems in social cognition and, importantly, these have been linked to problematic social functioning in daily life (Fett, Shergill, & Krabbendam, 2015; Green, Olivier, Crawley, Penn, & Silverstein, 2005; Penn, Sanna, & Roberts, 2008; Velthorst, Fett, et al., 2016). Many studies have investigated social cognitive processes separately. In this dissertation online social interactions, integrating different aspects of social cognition were addressed at the behavioural and neural level. Social decision-making paradigms were used in health, first-episode psychosis (FEP), and patients at clinical high-risk for psychosis (CHR). Increased understanding of the development of social skills in health, and during the development of a psychotic disorder may contribute to early detection of psychosis risk and to early intervention.

Social cognition & development

Social interactions with other people require social cognitive skills that facilitate the understanding of others, the building of relationships and trust. During human development from childhood to adulthood, social interactions with (close) others change. In healthy development, changes in interactions lead to development of social skills, in interplay with structural and functional maturation of the brain (Crone & Dahl, 2012; Steinberg, 2005), and in interplay with the (social) environment: Developing cognitive abilities and underlying neural circuitry allow for more complex social relationships, and in turn, changing social and environmental contexts shape social cognition and the underlying neural circuitry (Blakemore, 2012; Choudhury, Blakemore, & Charman, 2006; Nelson, Leibenluft, McClure, & Pine, 2005).

Most marked changes in the regulation of behaviour and emotions, and in the perception and evaluation of risk and reward occur during adolescence, a period of biological, cognitive and social changes (Steinberg, 2005). Adolescence starts at the onset of puberty, when important hormonal changes take place. This process of hormonal change causes remarkable physical changes. In parallel, the brain matures, causing changes in behaviour and cognition. Social cognitive development continues well into the twenties (Crone & Güroglu, 2013b; Dumontheil, Apperly, & Blakemore, 2010; Sowell, Thompson, Tessner, & Toga, 2001; Tamnes et al., 2010). While several studies investigated social decision-making in children, young adolescents and adults, data on the developmental processes from late adolescence into adulthood are still scarce (Frith & Frith, 2010).

Social interactions enable us to learn from others, find and maintain work, make friends and find a partner, provided these interactions are cooperative and pro-social. However, humans also display pro-social behaviour towards unknown others, even at the expense of themselves (Van Vugt & Van Lange, 2006). Humans might be intuitively

cooperative (Peysakhovich, Nowak, & Rand, 2014; Rand & Nowak, 2013), and positive social interactions may be inherently rewarding (Krach, Paulus, Bodden, & Kircher, 2010). Motivations to cooperate can largely differ (Balliet & Van Lange, 2013a; Haselhuhn, Kennedy, Kray, Van Zant, & Schweitzer, 2015; Powell & Van Vugt, 2003). Therefore, social interactions and cooperation do not only depend on whether these social cognitive skills are developed, (e.g., whether someone is able to recognise the wishes of another person), but also on the motivation to use these skills pro-socially (e.g., honouring or frustrating the other's wishes). This thesis will investigate both elements of social decision-making: the ability to perceive the perspective of others and react to their behaviour, and the motivation to use these skills in a given situation.

The social brain

The social brain network consists of a set of regions dedicated to social cognition (see S1).

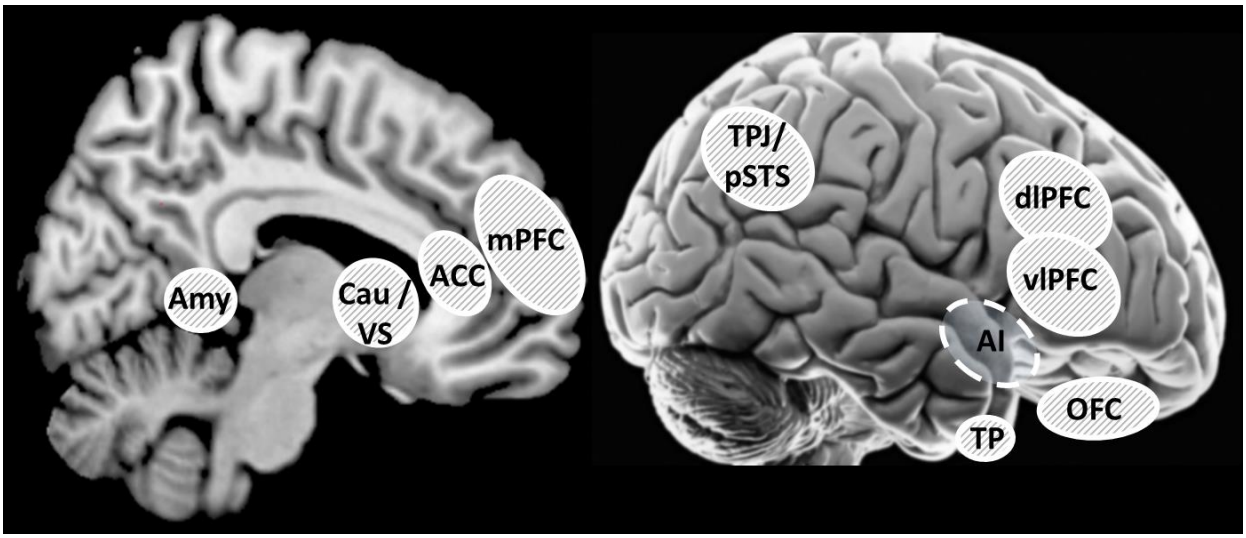

Figure 1: The Social Brain Network

ACC = anterior cingulate cortex; AI = anterior insula; Amy = amygdala; Cau/VS = caudate nucleus/ventral striatum; dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; TP = temporal pole; TPJ/pSTS = temporo-parietal junction/posterior superior temporal sulcus; vlPFC = ventrolateral prefrontal cortex.

These regions cover a large set of social cognitive functions, such as mentalising and theory of mind, empathy, and emotion processing, as well as reward learning and reward prediction. All these processes are required in social interactions and social decision-making (Rilling & Sanfey, 2011) and have extensively been studied with functional magnetic resonance imaging (fMRI). It comprises parts of the prefrontal and temporal lobes, insular cortex, ventral striatum, the caudate nucleus, and the amygdala.

The prefrontal regions include the medial (mPFC), dorsolateral (dlPFC), ventral (vMPFC), and orbitofrontal (OFC) prefrontal cortices, and the adjacent anterior cingulate cortex (ACC). The temporal regions include the posterior superior temporal sulcus (pSTS), the temporo-parietal junction (TPJ), and the temporal poles (Adolphs, 2009; Frith, 2007).

Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging is a non-invasive technique to measure function of the brain, using an MRI scanner. The strong magnetic field causes the hydrogen protons to align with this field. Radio frequency pulses are transmitted, and protons absorb the transmitted energy, causing them to flip, losing their alignment with the basic magnetic field. Interruption of the radio frequency pulses will make the protons flip back to their initial alignment, releasing the absorbed electromagnetic energy. This MR signal forms the basis of the scanned image. With fMRI changes of MR signal are measured, caused by the oxygenation level of the blood in a specific brain area. When a specific area is activated, energy is consumed, and initially the blood-oxygenation-level-dependent (BOLD) signal decreases. Consequently, the brain overcompensates the oxygen consumption by an increased inflow of oxygenated blood, resulting in an increase of BOLD signal. Multiple images are acquired in a short period of time, measuring the BOLD signal in every voxel in the brain (Huettel, Song, & McCarthy, 2004). For activation during a task, images acquired during the specific periods of interest are contrasted with periods with similar task activation, however not containing the cognitive process of interest, thereby filtering out all additional brain activation. Whole brain analyses investigate activation patterns throughout the entire brain, whereas region of interest analyses (ROI) investigate the activation within specific, predefined regions that are known or thought to be involved in the specific (cognitive) processes of interest.

Psychotic disorders and the psychosis continuum

Psychotic disorders are severe psychiatric disorders characterised by abnormalities in thought and perception. These disruptions cause patients to lose touch with reality. The core symptoms of psychosis are delusions (i.e., strongly held false beliefs, based on wrong conclusions of the outer reality) and hallucinations (i.e. sensory perceptions in the absence of external stimuli). Apart from positive symptoms, psychotic patients also show various cognitive impairments and deficits in social cognition. In parallel with the occurrence of positive symptoms, these cognitive impairments are not specific for psychotic illness: They also occur in other patient populations [e.g., patients with major

depression, bipolar disorder, obsessive compulsive disorder (Snyder, Miyake, & Hankin, 2015)], and are also found before the onset of the illness. The common way of diagnosing for psychotic disorders is the use of qualitative or semi-quantitative classification systems, in which people with "severe enough" symptoms are included and others, whose symptoms are less severe (and/or less frequent) are excluded from diagnosis (and eventually treatment due to health insurance requirements). Contrary to such a qualitative idea of symptoms, Johns and Van Os (2001) argued that there is evidence for continuity of psychotic symptoms: Patients differ from healthy subjects not in the type of symptoms they have (quality), but in the severity (quantity) of these symptoms. Besides, psychotic symptoms are not pathognomonic of psychotic disorders: 25% of patients with depression, bipolar or anxiety disorder experience psychotic symptoms, and they are also found in about 5% of the general population (Hanssen, Bak, Bijl, Vollebergh, & Van Os, 2005; Van Os & Murray, 2013), this is referred to as the psychosis continuum (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

Stages and markers of psychotic illness

Most cases of first psychotic episodes occur during adolescence, during mid/ late teens until early twenties (Kessler et al., 2007; Paus, Keshavan, & Giedd, 2008). Because behavioural and cognitive systems mature at different rates, adolescence is a period of increased vulnerability for developing psychopathology (Steinberg, 2005). Before the onset of psychosis, gradual, nonspecific changes in behaviour, thoughts and perceptions occur. However, these early warning signs can be difficult to distinguish from typical adolescent behaviour (Linszen et al., 2011). Many teens are difficult to motivate, to get up and do things, are not interested in learning for school, spend a lot of time on their own in their rooms (at the computer), and experience a rollercoaster of emotions. However, a worrisome drop in school or job performance; problems with concentration; suspiciousness or uneasiness with others; spending increasingly more time alone; and strong, inappropriate emotions or having no feelings at all are all early warning signs for psychosis.

With the aim of early prevention and intervention, more and more attention is directed to these warning signs in cognition and behaviour. Since first episodes usually occur during adolescence, prevention or delay of this first episode can decrease the detrimental impact on (normal) development. These studies include subjects at risk for developing psychosis, and the early stages of psychosis. Already 25 years ago, it was acknowledged that in the first five years after psychosis onset, deterioration of function occurred, and later levelled off. Research showed that early treatment can reduce the

number of relapses and yielded better prognosis (Birchwood & Macmillan, 1993). Later studies confirmed these findings, showing that early intervention in first-episode patients was associated with better outcome prognosis and better social and vocational functioning (Craig et al., 2004; Harris et al., 2005; Tang et al., 2014). Identification of early warning signs, biomarkers and endophenotypes for the risk for psychosis is crucial for early (and preventive) intervention. Better understanding of early warning signs can reduce the time of untreated psychosis, and therefore improve outcome prognosis (Marshall et al., 2005).

Relapses during psychotic illness are preceded by prodromal periods, where deterioration in functioning serves as a marker (Birchwood & Macmillan, 1993). Similarly, prodromal stages of a first episode have been characterised by nonspecific symptoms such as depressed mood and anxiety, negative symptoms, and sub-threshold or attenuated psychotic symptoms. However, prodromal stages can only be identified in retrospect of the illness. For predictive purposes, populations at high risk for psychosis have been identified. Individuals are at risk for psychosis when they 1) report attenuated psychotic symptoms (clinical high-risk); 2) they have experienced brief limited intermittent psychotic symptoms (BLIPS), i.e., transient psychotic symptoms with a duration shorter than one week; and 3) have a first degree relative with a psychotic disorder (genetic high-risk: Yung et al., 2003). The majority of clinical high-risk (CHR) individuals who display the same subclinical symptoms as patients in the prodromal stage will not transition to psychosis: they will have persistent subclinical symptoms or even recover spontaneously (Yung et al., 2005). In CHR, identification of the risk for transition will facilitate specific, personalised treatment, improving outcome and possibly delay (or prevent) transition to psychosis. More understanding of the factors that increase the risk for transition therefore is needed. This dissertation investigates the hypothesis that social cognitive deficits in FEP and CHR might serve as a marker for psychosis.

Social cognition in psychosis

Patients with psychosis show deficits in social cognitive skills, i.e. emotional processing, theory of mind (ToM) and mentalising, attribution style (inferring causes for events), and social perception and knowledge (Fett, Shergill, et al., 2015; Green et al., 2005; Penn et al., 2008). The development of these deficits differs per domain. Emotion processing disabilities seem to precede the disorder, showing deficits in CHR and siblings, and a decline with increasing duration of the illness (Green et al., 2008). However, others found emotion perception to be relatively intact in CHR, but declining with conversion to psychosis, and not during the course of the illness (Pinkham, Penn, Perkins, Graham,

& Siegel, 2007). Results with regard to ToM are more consistent, showing that ToM is affected prior to the onset of psychosis and also in unaffected siblings, both performing at a level in between healthy controls and patients. After conversion to psychosis ToM deficits remain relatively stable (Bora & Pantelis, 2013). Few data on attribution style are available (Van Donkersgoed, Wunderink, Nieboer, Aleman, & Pijnenborg, 2015), but attribution biases seem to be state related, therefore increasing with psychotic episodes (Green et al., 2008). This suggests that with the transition to psychosis, many social cognitive functions decline, stressing the need for early recognition and intervention.

Neural substrates for these behavioural impairments have been extensively studied. Schizophrenia patients show predominantly reduced activation in several areas of the social brain during a variety of cognitive tasks that tap into different social cognitive domains. Importantly, problems do not likely occur in isolated regions, but differences in activation are associated with reduced connectivity between regions within a network, possibly due to developmental changes (Green, Horan, & Lee, 2015; Schilbach et al., 2016). In real life interactions, social cognitive skills are not isolated, but used in conjunction. During emotion recognition tasks, patients showed reduced activation of the bilateral parahippocampal gyrus, amygdala, prefrontal and occipital regions (including fusiform gyrus), the cingulate cortex, thalamus, and caudate (Fett, Shergill, et al., 2015; H. Li, Chan, McAlonan, & Gong, 2009; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011; Taylor et al., 2012). Theory of Mind studies showed reduced activation in patients in the mPFC, medial frontal gyrus, posterior cingulate cortex, and temporal regions, including the superior temporal gyrus and temporal poles (Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Lee, Quintana, Nori, & Green, 2011; Pedersen et al., 2012). Reduced activation in similar regions has been found in empathy (Benedetti et al., 2009; Derntl et al., 2012). However, some studies also reported increased activation, pointing towards compensatory mechanisms, increased effort, and in some cases mistakenly attaching emotional salience to non-emotional stimuli (Mier et al., 2014; Mothersill et al., 2014; Pedersen et al., 2012; Taylor et al., 2012; Varga et al., 2013).

Neuroeconomic paradigms

Paradigms that were used in studies as described in the paragraph above tended to use offline measures of social cognition. While these are useful to isolate specific social cognitive skills, these skills occur in interplay in daily life. In the past decades, economic paradigms have been developed, to measure social cognition during online social decision-making, such as the ultimatum game (Güth, Schmittberger, & Schwarze, 1982), dictator game (Guala & Mittone, 2010), prisoner's dilemma (Axelrod & Hamilton,

1981), and the trust game (Berg, Dickhaut, & McCabe, 1995). The interdisciplinary field of neuroeconomics combines neuroscience, psychology, economics, and computational science to investigate how people make decisions (Sharp, Monterosso, & Montague, 2012). This combination enables us to study brain activity during real time online social interactions in a controlled environment (Tzieropoulos, 2013). In the past 15-20 years, neuroeconomic paradigms have been extensively studied in healthy individuals, and more recently research neuroeconomic methods have been applied in studying reward-related decision-making in psychiatric populations (Sharp et al., 2012). These paradigms require social cognitive skills such as mentalising, evaluation of (social) feedback, reward sensitivity and reward learning. Furthermore, although not directly assessed, they involve the motivation to engage in cooperative, pro-social interactions, the will to take the perspective of others into account, and to act accordingly. Two social decision-making paradigms formed the basis of this dissertation: the social mindfulness paradigm and the trust game. In the following, the concepts trust and social mindfulness will be discussed, followed by these social interactive tasks paradigms.

Trust

Trust is essential to initiate, establish, and maintain social relationships. It requires cooperation and reciprocity, especially in situations that involve a conflict between self and collective interests (Balliet & Van Lange, 2013b). A widely used paradigm to investigate trust, cooperation and reciprocity is the trust game [see Figure 2; (Berg et al., 1995)]. Here the first of two players, the investor, receives € 10 and can give any amount between € 0 and € 10 to the second player, the trustee. The given amount is tripled and the trustee then can return any part of this amount to the investor. In first instance the best payoffs for the trustee are reached by keeping the money. Thus, investing requires trust that a fair repayment will be made. In general, healthy adults trust others with at least half of the initial endowment (Johnson & Mislin, 2011; Tzieropoulos, 2013; Van den Bos, Van Dijk, Westenberg, Rombouts, & Crone, 2011), suggesting a natural tendency to cooperate. Iterative trust games with the same game partner do not only allow for the investigation of initial, so called baseline trust, but also for the investigation of the development of trust over consecutive trials (King-Casas et al., 2005).

During adolescence trust increases, individuals become more inclined to establish cooperation with unknown others (Fett, Gromann, Giampietro, Shergill, & Krabbendam, 2014; Sutter & Kocher, 2007). Furthermore, with age, first investments, i.e. baseline trust, and learning over trials increases (Van den Bos, Van Dijk, & Crone, 2012). After an increase of trust from childhood to mid-adolescence, slight decrease

towards early adulthood have also been reported (van den Bos, Westenberg, Van Dijk, & Crone, 2010). Evidence indicates that men are more trusting than women, both in single (Buchan, Croson, & Solnick, 2008; Croson & Gneezy, 2009) and repeated social interactions in the trust game (Balliet, Li, Macfarlan, & Van Vugt, 2011; Croson & Gneezy, 2009). However, the relation between gender and age on the development of trust is unknown.

Neural correlates of trust

A recent meta-analysis on neuroimaging studies using the trust game shows that particularly reward related areas are involved in the paradigm (Bellucci, Chernyak, Goodyear, Eickhoff, & Krueger, 2016). Differential activations are found in the investor and trustee, but here we will limit the discussion to the investor. Decisions to trust over multiple rounds consistently engage the ventral striatum, an area involved in signaling reward prediction errors. During the repayment phase, where the feedback is processed, the caudate is consistently activated, an area associated with reinforcement learning and with processsing relevant (social) information (Bellucci et al., 2016). Caudate activation correlated with the 'intention to trust', reflecting the development of a reputation of the game partner (King-Casas et al., 2005). Furthermore, mentalising is required to infer the other's intentions, in order to determine whether to trust the partner to reciprocate the displayed trust in future interactions (Gromann et al., 2013; Frank Krueger et al., 2007; Sripada et al., 2009).

Trust in psychosis

Trust game studies have shown that baseline trust is lower in patients than controls (Fett et al., 2016; Gromann et al., 2013). Both positive (Fett et al., 2012) and negative (Fett et al., 2016) symptoms have been associated with lower baseline trust, suggesting that reduced trust may reflect either paranoia or a lack of social motivation. The ability to learn from social feedback seems to depend on context (cooperative or unfair partner's responses) and illness duration: Early psychosis patients were able to adjust their trust to similar levels as controls (Fett et al., 2016), whereas chronic patients showed an insensitivity to positive feedback (Fett et al., 2012). In unfair interactions, early and chronic psychosis patients responded adequately to negative feedback (Campellone, Fisher, & Kring, 2016; Fett, Gromann, Shergill, & Krabbendam, 2015; Fett et al., 2012; Fett et al., 2016; Gromann et al., 2013). Studies in genetic high-risk individuals show that siblings' behaviour during the trust game was similar to controls. At the neural level, siblings showed reduced activation of the right caudate during investments, and the left insula during repayments (Gromann et al., 2014). The previous research findings

suggest that impairments in social reward related processing might be associated with the risk for psychosis, whereas deficits feedback learning only occur with longer illness duration. This dissertation will test whether reward related processing before and shortly after psychosis onset is still intact, presenting the first neural findings in first-episode psychosis, and the first trust data in patients at clinical high-risk for psychosis.

Social Mindfulness

Social mindfulness is "minding the needs and interests of others in a way that honours the idea that most people like to choose for themselves" (Van Doesum, Van Lange, & Van Lange, 2013). By behaving socially mindful, one maximises other people's control over their outcomes, granting them autonomy. This can be done by taking a step to the right in a narrow corridor, when you see someone approaching you rapidly, by helping someone to find his way to the experiment rooms despite your own plans or hurry, or by not taking the last piece of cheese cake if there are more pieces of chocolate cake left. In these examples, the other person will feel seen and acknowledged, and might even form a positive opinion about you. In the latter examples another aspect of social mindfulness becomes apparent: suspension of, or giving up your own preferences. Whether you are willing to do so, depends on (the importance of) the situation, and on the relationship you have, or want to build with the other person. One might argue that social mindfulness is just educated behaviour or norm compliance. Social mindfulness has exhibited reliable associations with self-reports of empathy, perspective-taking, honesty, and pro-social orientation (Mischkowski, Thielmann, & Glöckner, 2017; Van Doesum et al., 2013; Van Doesum, Van Prooijen, Verburgh, & Van Lange, 2016).

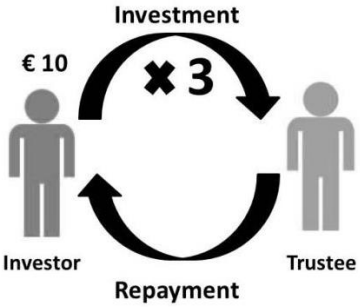

Figure 2: Trust Game

Figure 3: Social Mindfulness Paradigm

The social mindfulness paradigm (SoMi task) originates in the choice between a unique and a multiply present item (see Figure 3). In the SoMi task, four items are presented, identical (in value) but for one detail: Three green apples and one red apple; three mugs with stripes, one with dots. Participants are instructed that they always may choose an item first, which will not be replaced, and that after them, a second person may choose.

Choosing an identical item, and thereby leaving the second person a choice, is valued as socially mindful; taking away the unique item, and thus limiting this other person's choice, is called socially unmindful. Studies using the SoMi task have shown that spontaneously participants choose mindfully in around 60% of the trials, when playing with an unknown other. Social mindful behaviour seems to be independent of age (age range 18-86 years) and gender, although females score slightly more mindful (Van Doesum et al., 2013). SoMi, however, is higher in pro-socially orientated individuals; when the other player has a trustworthy face, is an in-group member, or someone liked (Van Doesum et al., 2013; Van Doesum et al., 2016); when the second person is perceived as lower in social class than the participant (Van Doesum, Tybur, & Van Lange, 2017). This dissertation will present the first neuroimaging data on social mindfulness, including first data in psychopathology. We expected regions of the social brain to be activated during SoMi decisions, and to find distinct activation patterns for mindful and unmindful decisions. We explored whether this basic form of cooperation was intact in FEP and CHR, despite the fact that these patients show deficits in social interactions. Contrasting the more complex forms of trust with basic forms of cooperation in SoMi may inform us about the extent of these social deficits.

Urbanicity

As stated above, healthy development, and development of psychotic disorders occur in an interplay of biological (genetic) factors, combined with the social and general environment. Urbanicity is the degree of population density of an area. This may vary from very rural to highly urban. Many studies on urbanicity use subdivisions of small villages – large towns. In the Netherlands, based on data from the national statistics bureau (CBS), urbanicity usually is defined by the number of inhabitants per km^2, using five stages (< 500 per km^2 - >2500 per km^2). The association between urbanicity and non-affective psychosis has been established by many epidemiological studies [for a review, see (Heinz, Deserno, & Reininghaus, 2013)], showing elevated incidence rates of psychosis in densely populated urban areas. Increased incidence rates of non-affective psychosis have been linked with urban birth (Laursen, Munk-Olsen, Nordentoft, & Bo, 2007; Mortensen et al., 1999), urban upbringing (Krabbendam & Van Os, 2005; Pedersen & Mortensen, 2001), and current city living (McKenzie, Murray, & Booth, 2013; Sundquist, Frank, & Sundquist, 2004). The effects of the population density seem particularly pronounced during upbringing (Heinz et al., 2013), as opposed to urban birth or current city living, suggesting a maximum impact of urban factors during sensitive developmental periods.

In the Western world, living in a city is associated with benefits like better (access to) health care, more employment opportunities, and better schools. Besides these benefits, city life also has disadvantages affecting physical wellbeing, as well as mental health and cognitive functioning (Attademo, Bernardini, Garinella, & Compton, 2017; Gouin et al., 2015; Lambert, Nelson, Jovanovic, & Cerdá, 2015; Stansfeld & Clark, 2015): Densely populated areas suffer from pollution, noise, and lack of green space (Attademo et al., 2017; Savale, 2014; Van den Berg et al., 2015). Urbanicity is often defined as a proxy for other social stressors, e.g., social deprivation (O'donoghue et al., 2016), lack of social capital, cohesion and trust (Drukker, Krabbendam, Driessen, & Van Os, 2006), disintegration of family networks and increased competition for resources (Zammit et al., 2010), being part of a minority group, perceiving group discrimination (Cantor-Graae & Selten, 2005; Kirkbride et al., 2007; Veling et al., 2008; Zammit et al., 2010), or feelings of being inferior (or different) to another person.

Studies in healthy individuals have tried to link their results to psychosis, indicating that urbanicity may impact on the hypothalamic–pituitary–adrenal (HPA) axis by means of increased social stress (Tost, Champagne, & Meyer-Lindenberg, 2015). Stress stimulates the HPA axis, altering hippocampal activity, which in turn affects the mesolimbic dopamine system. Dopamine and the limbic system are key to reward processes that are necessary for motivated behaviour and learning, for example in social interactions. Disruption of the HPA-axis is thought to lead to aberrant salience processing, where patients attribute meaning to otherwise irrelevant stimuli (Heinz & Schlagenhauf, 2010). A pioneer study investigating the influence of urbanicity on neural social stress processing showed that current city living was associated with higher activation of the amygdala during social stress, suggesting greater sensitivity to threat and negative emotions in city dwellers. Urban upbringing on the other hand, was associated with increased activity of the perigenual anterior cingulate cortex (pACC). The pACC is part of the limbic stress regulation system that is implicated in processing chronic social stressors (Lederbogen et al., 2011). Others found that current city living was associated with reduced activation in the left ventral tegmental area, a dopaminergic region modulating the midbrain dopamine system (Krämer, Diekhof, & Gruber, 2017). Furthermore, city living was associated with increased activity in the amygdala, medial orbital cortex and pACC during reward processing, supporting the possible role of urbanicity on dopamine disregulation. Although the authors suggested that these findings are also relevant for psychosis, these studies were conducted in healthy subjects. We investigated the association of urbanicity with social interactions directly in early psychosis.

Recently, attempts have been made to clarify the mechanisms underlying the epidemiologically well-documented association between urbanicity and psychosis at the neural level. Several studies have been published on the Dutch Genetic Risk and Outcome in Psychosis (GROUP) dataset, a large sample of more than 1000 non-affective psychosis patients, 1100 non-affected siblings, 900 parents, and 600 healthy controls (Frissen et al., 2017; Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015). These studies show that urban upbringing was unrelated to cell atrophy, structural differences in white matter, or cortical thickness. Resting state functional connectivity of the PCC, a seed region of the default mode network (DMN), and of the nucleus accumbens, a seed region for dopamine regulation within the meso-corticolimbic system, did not reveal significant associations with urban upbringing either (Peeters, Gronenschild, et al., 2015; Peeters, Van de Ven, et al., 2015). Summarising, it seems difficult to find associations of urbanicity with brain structure and connectivity. This thesis will investigate the association in an interactive social paradigm in psychosis, testing the hypothesis that urbanicity impacts on social interactions, both behaviourally and at the neural level, attempting to find underlying neural mechanisms that can explain the association.

The aims of this dissertation

This dissertation addresses the neural correlates of social cognition during social decision-making in different contexts, in health, first-episode psychosis (FEP), and patients at clinical high-risk for psychosis (CHR). Two neuroeconomic paradigms were used to investigate social cognition in an online setting, while interactions took place. Part I investigates the neural correlates of social mindfulness in health and psychosis; Part II aimed to study gender specific developmental changes of trust in late adolescence and early adulthood. Additionally, trust game data on FEP and CHR are added to the psychosis literature, covering the entire developmental pathway to psychosis. Part III intended to describe the neural correlates of the association between urbanicity and psychosis, in a literature review and a trust game study.

Outline

This dissertation consists of one review study, and five fMRI studies, based on a dataset, including 29 FEP, 18 CHR, and 53 healthy controls. Participants were in late adolescence and early adulthood (aged 16-29). They performed two tasks in the MRI scanner. Part I (chapters 2 and 3) discusses the SoMi paradigm, and part II (chapters 4 and 5) concerns the trust game, with one study each conducted in healthy individuals, and FEP and CHR patients, respectively. Part III (chapters 6 and 7) provides a review of the neural correlates of urban risk environments in health and psychosis and investigates the association between urbanicity and psychosis at the neural level using the trust game.

Chapter 2 is the first study mapping the neural correlates of social mindfulness in a sample of 47 healthy adolescents and young adults (age 16–27). The study describes how the SoMi task contributes to the neuroeconomic literature, and investigates condition specific neural activation for socially mindful and unmindful choices. Neural outcomes are correlated with social value orientation, a mentalising task, and participants' SoMi index, to evaluate to what extent *skill* and *will* contribute to the neural activation.

Chapter 3 describes differences in behavioural and neural outcomes of the SoMi task between healthy controls, FEP and CHR. Adding low-cost cooperation and pro-social interactions to the (high-cost) social decision-making literature of psychosis may shed a light on which level of cooperation is affected or still intact in different illness stages.

Chapter 4 examines the role of age and gender on the development of trust in 43 healthy late adolescents and young adults (16–27 years, 22 male). Many studies consider participants as adults after the age of 21. Brain maturation, however, continues well into the twenties. This study investigates gender specific development of trust throughout a broad developmental window, in cooperative and unfair interactions.

Chapter 5 uses the same paradigm to examine whether trust is equally reduced in FEP and CHR as in chronic patients, or whether trusting behaviour is still intact in pre- and early stages of the illness. Additionally associations with symptom severity are explored.

In **Chapter 6** FEP and CHR are grouped into one sample of patients, to investigate the association between urban upbringing and trust in patients with psychotic symptoms. Urbanicity is defined as the population density per postal code, and in a later stage dichotomised in higher- and lower urban upbringing. Earlier studies in healthy participants have found a link between urbanicity and social stress. This study is the first to investigate urbanicity in psychosis using an interactive paradigm with functional MRI.

Chapter 7 reviews the existing literature on neural correlates of urban risk environments. The association between urbanicity and psychosis is well established, but the underlying neural mechanisms of this association are largely unknown. Structural and functional neuroimaging research is reviewed, and alternative explanatory mechanisms are investigated.

In the general discussion, **Chapter 8**, the main findings of the studies are presented and combined into a broader perspective. The chapter considers the strengths and weaknesses of the studies described in the previous chapters, and concludes with directions for future research.